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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,589	01/15/2004	Keizo Koya	3211.1001-001	5403

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,589	KOYA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18-29;35,38 and 39* is/are allowed.

6)☒ Claim(s) *1-17 and 30-34* is/are rejected.

7)☒ Claim(s) *36-37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 12/22/2006, have been fully considered and are deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. However, upon further consideration the following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. In light of the new rejection being applied against the instant claims, this Office Action is **Non-Final**.

Status of the Claims

Claims 1-39 are currently pending and are the subject of this Office Action. Claim 18 is presently amended and claims 36-39 are newly presented.

Response to Arguments

Applicant's arguments, see Response (pages 15-16), filed 12/22/2006, with respect to the Obvious-Type Double Patenting rejections of claims 18-29 and 35 have been fully considered and are persuasive. The rejection of claims 18-29 and 35 has been withdrawn. The previous Office Action (mailed 9/22/2006) set forth Obvious-Type Double Patenting rejections over U.S. Patent Nos. 6,800,660, 6,762,204, 7,001,923 and 7,037,940. These patents all claim methods of treating cancer comprising administering the instantly claimed compounds in combination with taxol or a taxol analog. In the Amendments filed 12/22/2006, Applicants amended instant claim 18 to specifically exclude the administration of taxol or a taxol analog. As such, the instant claims no longer overlap in scope with the above patents.

However, upon further consideration, the Examiner is reapplying the Scope of Enablement rejection first raised in the Office Action mailed 11/3/2005. In response to the original Scope of Enablement rejection, Applicant's argued that they have shown unexpected results in the treatment of multi-drug resistant leukemia, sarcomas and melanomas. While this argument is persuasive for these specific cancers, in view of the broad scope of the claimed subject matter, these results do not provide any reasonable expectation that the claimed genus of compounds could be predictably used to treat other multi-drug resistant cancers.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 30-34 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of multi-drug resistant leukemia, uterine sarcoma and melanoma, does not reasonably provide enablement for the treatment of all multi-drug resistant cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of multi-drug resistant cancers comprising administering a compound from the genus recited in claim 1. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gura *et al.* (Science, 1997, 278:1041-1042) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Gura *et al.*, cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers. Further, while the art of treating cancer is generally unpredictable, treating multi-drug resistant cancers is even more unpredictable. By their very nature, multi-drug resistant cancers are not susceptible to treatment with traditional chemotherapeutic agents because these cancers have developed resistance to such treatment. Thus, *a priori*, one skilled in the art would not expect a drug used to treat cancer to be effective in treating a multi-drug resistant cancer. As such, it is in no way predictable that any given chemotherapeutic drug will be efficacious in treating multi-drug resistant cancer.

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of multi-drug resistant cancers by administering a compound selected from a very broad genus of compounds with multiple substituents. Others, such as claims 4 and 17, are narrower, reciting specific sub genera and species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of multi-drug resistant cancer with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimen (dosages, timing, administration routes, etc.) necessary to treat all multi-drug resistant cancers, particularly in humans. The specification adequately describes methods

of synthesizing the claimed compounds and further demonstrates that: 1) one specie (Compound 1) is effective against a single multi-drug resistant melanoma cell line and a single leukemia cell line *in vitro* (Table 1) and 2) 18 species of the claimed genus are effective against a single multi-drug resistant uterine sarcoma cell line *in vitro* (Table 2). However, only one compound (Compound 16) was shown to be effective *in vivo* against uterine sarcoma. Breast cancer is a type of cancer known in the art to develop resistance to chemotherapy. However, there is no evidence that the claimed genus (or even a single specie from said genus) is effective in treating multi-drug resistant breast cancer. Thus, the applicant at best has provided specific direction or guidance only for the treatment of multi-drug resistant leukemia, uterine sarcoma and melanoma. No reasonably specific guidance is provided concerning useful therapeutic protocols for any other multi-drug resistant cancers.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for a reasonable number of multi-drug resistant cancers as inferred in the claims and contemplated by the specification. Applicants have not correlated structural features with activity in inhibiting or treating multi-drug resistant cancers. Further, there is no evidence that the claimed compounds are effective against carcinomas. The treatment of carcinomas is often different than the treatment of sarcomas (cancer of the connective or supportive tissue). As such, it is not predictable, and would require undue experimentation, to determine effective

compounds and treatment regimens for carcinomas given the guidance provided in the specification. For example, without knowing the mechanism through which the claimed compounds are able to overcome multi-drug resistance, it is not possible to predict what structural features are required to maintain effiacy. The compounds that have been shown to be efficacious (e.g., compounds 1-18 as shown in Figure 1) are all structurally similar. These compounds have similar substituents and all contain a dicarbonyl (*i.e.* Z is O). However, the claims contemplate Z forming an aromatic ring. Such compounds (*e.g.* claim 4) may not be effective. As such, given the broad scope of the claims and the guidance provided in the specification, the skilled artisan would be faced with undue experimentation to practice the claimed invention.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 5-11, 13-19, 22-28 and 30-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-29 of copending Application No. 11/157,213. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds recited in the claims of the '213 application encompass the compounds of the instant claims when the instant compounds are "a pharmaceutically acceptable salt thereof". The salts recited in the '213 application are resonance forms of the instantly claimed compounds. As such, the instant claims and the claims of the '213 application are commensurate in scope when a salt of the instant compounds is administered to treat cancer.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

Claims 18-29, 35 and 38-39 are allowable over the prior art of record.

Claims 36-37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 1-17 and 30-34 are rejected under 35 U.S.C. 112, 1st Paragraph (Scope of Enablement) but are free of the prior art of record. Claims 18-29, 35 and 38-39 are allowable over the prior art of record. Claims 36-37 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

March 21, 2007

Phyllis Spivack
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PRIMARY EXAMINER
3/21/07